IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent Application of:
Murray, *et al.*

Application No.: 10/587,313

Filed On: April 28, 2008

For: BONE MORPHOGENIC PROTEIN BINDING PEPTIDE

Examiner: David S. Romeo

Conf. No.: 4686

Art Unit: 1647

DECLARATION UNDER 37 C.F.R. 1.132

Commissioner for Patents
Alexandria, VA 22313-1450

Dear Sir:

I, Keyvan Behnam, Ph.D., hereby declare as follows:

1. I am a co-inventor of U.S. Application No. 11/791,940.

2. I am currently the Chief Scientist at Lanx, Inc., a company specializing in medical devices. I received my Bachelor of Science degree in Bioengineering from University of California, Berkeley. I received my Ph.D. in Physiological Science from the University of California, Los Angeles.

3. The present invention relates to BBP, a substantially purified peptide comprising the amino acid sequence of SEQ ID No: 1 or a fragment thereof, wherein the fragment increases the degree or rate of osteogenesis or calcification. BBP is a 19 amino acid, 2.1 kD peptide that is derived from a 18.5 kD fragment of the substantially longer 24 kDa secreted phosphoprotein Spp-24.

4. Peptides and proteins are composed of amino acids. The shape, or conformation, based on folding, of a peptide is determined by its amino acid sequence. This is because the amino acid side chains associate with each other and with water to form weak bonds. Through this process, forces are developed that make particular conformations especially

stable for a given peptide. *See, e.g.*, Alberts, B., *et al.*, *The Molecular Biology of the Cell, Second Edition*, pp. 107-124 (1989).

5. After a peptide folds into the favorable conformation, the amino acid residues that remain exposed on the surface of the peptide are able to form weak bonds and/or interact with other molecules. Additionally, the overall size of the protein or peptide, as well as the orientation of exposed amino acid side chains relative to one another may influence the ability of the peptide to bond to other molecules. Thus, the manner in which a peptide functions is determined by the size and conformation of the peptide, which in turn is determined by the amino acid sequence. *See, e.g.*, Alberts, B., *et al.*, *The Molecular Biology of the Cell, Second Edition*, pp. 107-124 (1989). Thus, peptides that contain different amino acid sequences may have different sizes and structures and function differently.

6. I have reviewed the Advisory Action mailed July 14, 2011. I have also reviewed U.S. Patent No. 5,620,867 ("Keifer") and WO 96/21006 ("Price"). In the Advisory Action, the Examiner states that Keifer and Price disclose a peptide that comprises the amino acid sequence of SEQ ID No: 1. The Examiner further states that as a result, Keifer and Price disclose a peptide comprising SEQ ID No: 1, or a fragment thereof, that increases the degree or rate of osteogenesis or calcification.

7. In Figure 3, Keifer discloses a peptide that includes in part the amino acid sequence for the SEQ ID No: 1 fragment ("BBP"). In Figure 5, Price discloses a peptide that includes in part the amino acid sequence for BBP. However, neither Keifer nor Price discloses the peptide BBP. Instead, the fragment is disclosed as part of a substantially larger protein. In fact, Figure 3 of Keifer and Figure 5 of Price disclose the amino acid sequence of secreted phosphoprotein-24 (Spp-24). *See* Brochmann, E. J., *et al.*, *Bone morphogenetic protein-2 activity is regulated by secreted phosphoprotein-24 kd, an extracellular pseudoreceptor, the gene for which maps to a region of the human genome important for bone quality*, 58 Metabolism 644 (2009)("Brochmann 2009"). The size, folding, and function of Spp-24 differs greatly from BBP. The Brochmann 2009 article is attached as Exhibit A to my Declaration.

8. The full-length Spp-24 protein disclosed in Figure 3 of Keifer and Figure 5 of Price, contains 203 amino acid residues. The first 23 amino acids comprise a leader sequence that is excised to form a 180 residue, 20.5 kDa protein. *See* Brochmann 2009, at p. 606. In contrast, BBP comprises a 19 amino acid, 2.1 kDa peptide fragment (residues 107-126). *See* Specification, at Figures 1A, 1B.

9. In the study described in Brochmann, E.J., *et al.*, *Carboxy terminus of secreted phosphoprotein-24 kDa (Spp24) is essential for full inhibition of BMP-2 activity*, 28 J. Orthopedic Research 1200 (2010)("Brochmann 2010"), four different proteins comprising different fragments of the Spp-24 protein were tested to determine their impact on bone formation when administered in combination with BMP-2. The four proteins tested were the 20.5 kDa Spp-24 (residues 24-203), Spp18.1 (residues 24-176), Spp16.0 (residues 24-157), and Spp14.5 (residues 24-143). *See* Brochmann 2010, at pp. 1200-1201. Various portions of the C-terminus region of full-length protein were excised to make the 4 proteins described above. The results of the study showed that both the Spp-24 and the Spp14.5 proteins, administered at a dose of 2.5 mg, inhibited bone formation. The Spp-24 protein completely inhibited bone formation, while Spp-14.5 reduced bone formation. When administered at 2.5 mg, the Spp18.1 and Spp-16.0 proteins had no effect on bone formation. When administered at lower doses of 0.5 mg and 0.05 mg, the Spp16.0 and Spp-18.1 proteins slightly increased bone formation, but the results were not statistically significant. The Spp-24 and Spp14.5 proteins, when administered at the lower doses, slightly inhibited bone formation, but the results were not statistically significant. *See* Brochmann 2010, at p. 1202. Note that all of these proteins contain the SEQ ID No: 1 sequence. *See* Brochmann 2010, at p. 1201. The Brochmann 2010 article is attached as Exhibit B to my Declaration.

10. As described above, various fragments of the Spp-24 protein have differing effects on bone formation when administered with BMP-2. The Spp-24 protein (residues 24-203) and the Spp-14.5 protein completely inhibit bone formation when administered in large doses. *See* Brochmann 2010, p. 1202. The Spp18.5 and Spp16.0 proteins have no effect on bone formation when administered in large doses and exhibit a small but not statistically significant increase in bone formation when given in lower doses of 0.5 mg

and 0.05 mg. In contrast, the claimed BBP produces a statistically significant increase in bone formation when administered in a 0.5 mg dose along with BMP-2. *See* Specification, Example 2.

11. Therefore, fragments of the Spp-24 protein of various lengths have been shown to exhibit different effects on bone formation when administered with BMP-2. It is thus not the case that any amino acid sequence containing SEQ ID No: 1 will increase bone formation. Thus, the presence of an amino acid sequence within a larger protein is not predictive of a claimed function.

Respectfully submitted,

Keyvan Behnam

Dated: 7/15/11

Keyvan Behnam, Ph.D.

Enclosures:

Brochmann, E. J., *et al.*, *Bone morphogenetic protein-2 activity is regulated by secreted phosphoprotein-24 kd, an extracellular pseudoreceptor, the gene for which maps to a region of the human genome important for bone quality*, 58 Metabolism 644 (2009).

Brochmann, E.J., *et al.*, *Carboxy terminus of secreted phosphoprotein-24 kDa (Spp24) is essential for full inhibition of BMP-2 activity*, 28 J. Orthopedic Research 1200 (2010).